"NEUROPATHIC SYMPTOMS WITH SARS COV-2 VACCINATION" A REVIEW

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SYMPTOMS OF SMALL FIBER NEUROPATHY

- Pain and burning in the lower and upper extremities
- "Pins and needles"
- Loss of feeling in the hands and feet
- Feet and hands are tender or sore
- Cramping in feet, ankles, calves, and hands
- Numbness
- Fatigue
- Inability to sweat
- Dry eyes
- Skin discoloration
- Dizziness, lightheaded
- Difficulty breathing
- Increased heart rate
- Difficulty with bowel and bladder functions
DYSAUTONOMIA

**PUPILOMOTOR**
- impaired pupil response (uncomfortable in bright light)
- difficulty with vision

**SECRETOMOTOR**
- difficulty sweating, tearing and other fluid production (dry eyes, dry mouth, difficulty swallowing, dry skin)

**GASTROINTESTINAL**
- nausea, vomiting, diarrhea, constipation, abdominal pain, reflux, heartburn, impaired motility

**NEUROLOGICAL**
- migraine, cognitive deficits, brain fog & mental clouding

**PULMONARY**
- shortness of breath
easily winded
difficulty breathing

**CARDIOVASCULAR**
- palpitations, chest discomfort
- high heart rate (tachycardia)
- low heart rate (bradycardia)
- high or low blood pressure
- abnormal blood vessel functioning
- blood pooling

**URINARY**
- difficulty with urine retention and/or excretion

**ORTHOSTATIC INTOLERANCE**
- difficulty standing still, fatigue, lightheadedness,
increase in symptoms with upright posture,
fainting (syncope) or near-fainting, pallor

**Symptoms can be**
**SUDDEN and unpredictable**
in onset
NEUROPATHIC SYMPTOMS WITH SARS COV-2 VACCINATION

NIH – National Institutes of Health [LINK TO STUDY]
Avindra Nath MD, Farinaz Safavi MD, Lindsey Gustafson NP, Brian Walitt MD MPH, Tanya Lehky MD, Amanda Weibold RN, Yair Mina MD

Sara Debashi, MD

Susan Shin, MD

Baohan Pan, MD, Michael Polydefkis, MD

Anne Louise Oaklander, MD PhD
"Various peripheral neuropathies, particularly those with sensory and autonomic dysfunction may occur during or shortly after acute Covid-19 illnesses. These appear most likely to reflect immune dysregulation. If similar manifestations can occur with the vaccination remains unknown.

"This observational study suggests that a variety of neuropathic symptoms may manifest after SARS-COV-2 vaccinated and in some patients might be an immune-mediated process..."

"...Further investigation is required to explore underlying mechanisms and targeted therapies for these neurologic disorders."
DEMOGRAPHICS

23 PATIENTS REPORTING NEW NEUROPATHIC SYMPTOMS BEGINNING WITHIN 1 MONTH AFTER SARS-COV-2 VACCINATION

92% Female
2 male – 21 female

Median age 40 years
Age range from 27-69 years old

100% reported sensory symptoms

61% had orthostasis, heat intolerance and palpitations

0% had previous neurological illness

52% had objective evidence of small-fiber peripheral neuropathy
OBJECTIVE FINDINGS

AUTONOMIC AND NEUROPATHY

**Autonomic**
- 7 of 12 had reduced distal sweat production
- 6 of 12 had positional orthostatic tachycardia syndrome

**Small Fiber Neuropathy**
- 16 lower leg biopsies –
  - 31% had diagnostic/subthreshold epidermal neurite
  - 13% were borderline
  - 19% showed abnormal axonal swelling

**Electrodiagnostic**
- Test results were normal in 94%

**Imaging** – 100% of MRIs were normal
Randomly selected five patients that were evaluated for immune complexes showed decomposition of complement C4d in endothelial cells.
The complement system, also known as the complement cascade, is a complex process that is part of the immune system. In laymen’s terms, it is a defense system comprised of proteins and enzymes designed to clean our bodies of microbes and damaged cells, and cellular debris. For example, when a foreign antigen (say a virus or viral particle) enters the body, these surveillance proteins recognize the foreign invader and begin a cascading alert system. This can be compared to one person seeing a fire, then telling another person who tells another, who then alerts the fire department. Along this process a series of enzymatic reactions happen. If this system is overwhelmed dysfunction can occur. In some cases this can lead to a “dysimmune response”.

In the case of the NIH study, the sub-complement C4d, was found in endothelial cells or cells that line vessels. C4d is a microscopic protein that is “sticky” and thus adheres tightly to endothelial cells. This was an important finding in the study and a probable cause of the small fiber neuropathy seen in the covid-19 vaccine injuries. The resulting neuropathy symptoms are caused by C4d getting “stuck” at the blood-nerve-barrier.

Vessels and nerves run parallel as nerves need blood supply. If the complement system breaks down (by being suddenly overwhelmed by production of spike protein) an error can occur where C4d production continues and the system’s ability to self-regulate is inhibited. Once C4d is circulating and enters the micro-circulation such as capillaries that feed nerve, blood supply to the nerves may be cut off. The result of this is neuropathic pain as the small nerve fibers are damaged or die. Halting this dysimmune process is critical to restore normal nerve function. It is critical to intervene early to limit nerve damage and dysfunction. Intravenous immunoglobulin therapy has been shown in studies to be an effective treatment to modulate the immune system.
BLOOD-NERVE BARRIER
The blood-nerve barrier is a physiological boundary between the peripheral nerve axons and the bloodstream that prevents the transfer of substances from the plasma to the nerve fibers. It is similar to the blood-brain barrier. There is selective permeability to solutes within the endothelial cells of the endoneurial continuous capillaries and in the internal layers of the perineurium.

Endothelial cells from endoneurial vessels joined tightly together by specialized junctions minimize capillary permeability. Adjacent to the capillaries, the perineurial sheath is composed of large numbers of tight junctions between the perineurial cells, isolating each fascicle from the interfascicular and epineurial environment. The blood-nerve barrier maintains and guarantees axonal function in the peripheral nerves.

Blood–Brain Barrier
The BBB and blood–nerve barrier represent dynamic, tightly regulated interfaces that separate nervous tissue from many blood-borne materials. The BBB consists mainly of specialized capillary endothelial cells in which the presence of complex tight junctions...Glial cell processes (mainly astrocytic) are also implicated in the regulation, maintenance, and repair of these barriers.

https://www.sciencedirect.com/topics/neuroscience/blood-nerve-barrier#~:text=The%20blood-nerve%20barrier%20is%20a%20physiological%20boundary%20between,fibers.%20It%20is%20similar%20to%20the%20blood–brain%20barrier.
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"All our patients had neuropathic symptoms but objective findings of SFN were present in a few patients only."

"Anti-spike protein immune responses may link post-Covid and post-vaccine syndromes."

"In studies of mouse sensory ganglia, small-fiber neurons preferentially display the ACE-2 docking protein for SARS-COV-consistent with a potential predominance of SFN."
LIMITATIONS AND CONSIDERATIONS:

• Small patient population, limited by an observational study.

• Evaluation for a short period of time

• Did NOT rule out possible vaccine involvement

• Future studies are needed:
  • Skin Biopsies to look for C4d
  • Auto-Antibodies
  • Study with larger population, longer duration
  • Neuro-specific studies are needed